Application of the Sharpless Asymmetric Dihydroxylation Methodology to the Enantioselective Preparation of 2,3-Dihydroxytetrahydro-2-naphthoic Esters

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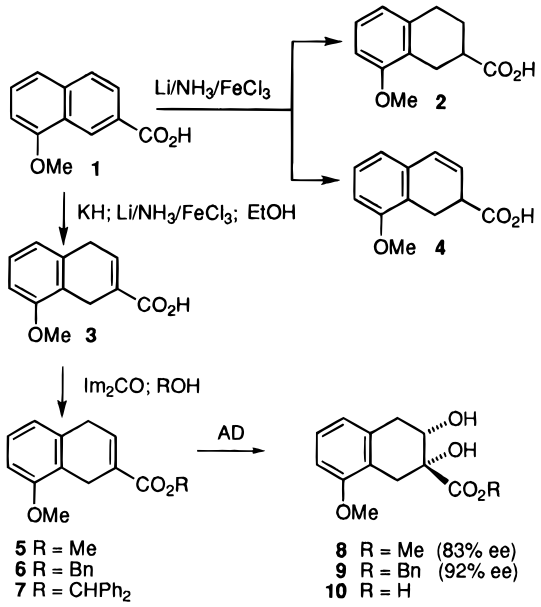
Dihydroxytetrahydronaphthoic acid **10** was envisaged as a key starting material in the total synthesis of C-ring functionalized gibberellins following established strategies.[1−3] In this paper, we describe the successful application of the Sharpless asymmetric dihydroxylation (AD) methodology[4] to the development of an efficient, enantioselective route to **10** from the dihydronaphthoic ester **6**. While there are a number of methods available for the synthesis of 1,4-dihydronaphthoic acids,[5] the procedure developed by Subba Rao for the controlled Birch reduction of 2-naphthoic acids attenuated by ferric chloride appeared to be the most synthetically useful.[6] However, simple application of the published protocol (which had been reported to afford 75% yields of the 1,4-dihydro derivatives in related examples) to the reduction of 8-methoxy-2-naphthoic acid (**1**)[7,8] afforded an inseparable mixture of four compounds, with the three major products being the 1,2-dihydro isomer **4**, the over-reduced tetrahydro acid **2**, and starting material (Scheme 1). Only a trace of the desired 1,4-dihydro isomer **3** could be observed in the ^{1}H NMR spectrum of the mixture.

The presence of large quantities of **2** seemed to suggest that the presumed intermediate dihydro enolate was being protonated during the reaction and then underwent further reduction, an outcome that could be attributed to the ammonium ions generated on addition of the naphthoic acid to the liquid ammonia. When the Birch reduction was carried out on the potassium salt of the acid[10,11] followed by an ethanol quench, **3** and **4** were

Scheme 1



obtained in a 7:3 ratio. With an evaporation time of 5 h, the ratio was improved to 92:8.[12]

The derived methyl ester **5** was susceptible to oxidation and had to be used relatively quickly; even so, methyl 8-methoxy-2-naphthoate was an inseparable contaminant (5%). From the stereoselectivity rules described by Sharpless for the AD reaction,[4] it was concluded that use of the $(DHQ)_2$−PHAL ligand should give the desired enantiomer corresponding to the gibberellin absolute configuration,[3] but the reaction using the commercially available[13] AD mix-α was sluggish, with only 20% reaction after 48 h at room temperature. The use of a modified AD α-mixture,[4b,14] comprised of 1 mol % osmium and 2 mol % ligand, however, resulted in complete reaction after 5 h at 4 °C, affording the diol **8** in 85% yield (Scheme 1).[15] The ee of the AD was determined to be 83% by ^{19}F NMR analysis of the mono-Mosher ester,[16,17] a disappointing result in view of outcomes with similar substrates.[18]

Sharpless and co-workers, investigating the kinetics of the AD, had found that $(DHQD)_2$−PHAL gave excep-

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(1) Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626.
(2) King, G. R.; Mander, L. N.; Monck, N. J. T.; Morris, J. C.; Zhang, H. *J. Am. Chem. Soc.* **1997**, *119*, 3828−3829.
(3) Mander, L. N. *Chem. Rev. (Washington, D.C.)* **1992**, *92*, 573.
(4) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation, In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, Germany, 1993; pp 227−272.
(5) (a) Baeyer A.; Besemfelder, E. *Justus Liebigs Ann. Chem.* **1891**, *266*, 187. (b) Derick, C. G.; Kamm, O. *J. Am. Chem. Soc.* **1916**, *38*, 400. (c) Colver, C. W.; Noyes, W. A. *J. Am. Chem. Soc.* **1921**, *43*, 898. (d) Monododoev, G. T.; Przhiyalpovskay, N. M.; Belov, V. N.; *J. Org. Chem. USSR.* **1965**, *1*, 1257. (e) Ishikawa, T.; Yamato, M. *Chem. Pharm. Bull.* **1982**, *43*, 898.
(6) Murthy, A. R.; Sundar, N. S.; Subba Rao, G. S. R. *Tetrahedron* **1982**, *38*, 2831.
(7) The majority of the literature methods[8] for the synthesis of **1** are not synthetically useful, as a key intermediate is 2-aminonaphthyl-8-sulfonic acid, which can only be prepared in low yield.[8e,9] A more efficient synthesis was achieved starting from 1,7-dimethoxynaphthalene, and the details are presented in the Supporting Information.
(8) (a) Jacques, J. *Mem. Pres. Soc. Chim.* **1953**, 185. (b) Adcock, W.; Wells, P. R. *Aust. J. Chem.* **1965**, *18*, 351. (c) Loewenthal, H. J. E.; Gottlieb, L. *J. Org. Chem.* **1992**, *57*, 2631. (d) Horii, Z.; Matsumoto, Y.; Momose, T. *Chem. Pharm. Bull.* **1971**, *19*, 1245. (e) Schreiber, K. C.; Byers, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 859.
(9) (a) Mueller, A. C.; Hamilton, C. S. *J. Am. Chem. Soc.* **1944**, *66*, 860. (b) Royle, F.; Schelder, J. *J. Chem. Soc.* **1923**, 1649.
(10) Mander, L. N. in *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: 1991; Vol 8, pp 489−522 and references therein.
(11) Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* **1982**, *23*, 1095.
(12) Elimination of the ethanol quench led to the isolation of the 1,2-dihydro acid as the major product (64% yield), indicating that the ethoxide anion generated from the ethanol is a sufficiently strong base to abstract the hydrogen α to the carboxylate anion. The 1,4-dihydro acids are reported[5a−c] to be the more stable of the two isomers, so given time, the equilibrium will favor the thermodynamically more stable product.
(13) Available from Aldrich Chemical Co.
(14) Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2079.
(15) For comparative purposes, the racemate was obtained by carrying out the identical reaction, in the absence of ligand, to afford (±)-**8** in 89% yield. This reaction was appreciably slower, taking 18 h at room temperature.
(16) The Kakisawa modification[17d] of the Mosher method[17a−c] was employed; details are provided in the Supporting Information. When the Kakisawa procedure was followed to completion, the absolute configuration at C3 was determined to be *S*. As the dihydroxylation is stereospecific, this means that the absolute stereochemistry at C2 must be *R*. As expected, the absolute configuration matches that predicted by the Sharpless stereoselectivity rules.

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tionally high rate constants with aromatic substrates.[19] These outcomes were attributed to the presence of a "binding pocket", set up by the aromatic rings of the ligand, which enabled especially good transition-state stabilization for aryl-substituted alkenes within the pocket. The benzyl and the diphenylmethyl esters (**6** and **7**) were therefore investigated to see if any worthwhile improvements in the ee could be obtained from the AD. The long reaction times required to synthesize these esters meant that aromatization, a minor problem in the formation of **5**, became a major issue. However, it was discovered that the benzyl ester **6** was formed rapidly with only minor aromatization when a variant of a method developed by Ohta and co-workers for the synthesis of *tert*-butyl esters was used.[20] Thus, reaction of acid **3** with *N*,*N*-carbonyldiimidazole, followed immediately by treatment with benzyl alcohol in the presence of DBU, afforded the desired benzyl ester **6** in 90% purity in ca. 83% yield. The AD on the benzyl ester afforded diol **9** in 74% yield (82% based on pure starting material) with an ee of 92%, from which material of high optical purity could be obtained after one recrystallization from ether. The diphenylmethyl ester **7** was also prepared to determine if the ee could be further improved, but it proved to be unreactive to all variations of the AD. Apparently, the diphenylmethyl ester group is too bulky to allow the osmium complex to reach the alkene bond.

In summary, a reliable procedure for the reduction of 8-methoxynaphthoic acid to the 1,4-dihydro derivative has been developed and should be general for most 2-naphthoic acids. The objective of obtaining enantiopure 2,3-dihydroxy-8-methoxy-1,2,3,4-tetrahydronaphthoic acid has been realized and, again, the methodology should be extendable to analogous products. Access to the 2- and 3-monohydroxy analogues by standard deoxygenation methods[21] can also be envisaged, thereby expanding the number of options for gaining access to enantiopure hydroxylated tetrahydronaphthoic acids.[22]

Experimental Section[23]

1,4-Dihydro-8-methoxy-2-naphthoic Acid (3). Dry THF (17 mL) was added to a mixture of the acid **1**[7] (1.01 g, 5.0 mmol) and KH (200 mg, 1 equiv) under nitrogen. Hydrogen was immediately evolved. After 1 h, anhydrous $FeCl_3$ (50 mg, 5 wt %) was added to the thick white suspension. Ammonia (predried over Na, 100 mL) was distilled into the precooled flask at −78 °C (acetone/dry ice). Upon completion of the distillation, the bath was removed and small pieces of lithium wire (263 mg, 7.5 equiv) were added over a period of 45 min at −33 °C. The solution was stirred for 10 min after addition of the lithium and then dry EtOH (2.5 mL) was added dropwise. The ammonia was allowed to evaporate over a period of 5 h under a slow stream of nitrogen. The residue was dissolved in water and this was acidified to pH 1 with concentrated HCl. The suspension was extracted with EtOAc (×3). After washing with water and brine, the solvent was removed in vacuo to afford a white solid. ^{1}H NMR spectroscopy revealed a 92:8 mixture of **3** and 1,2-dihydro acid **4**. Recrystallization of the mixture from EtOAc gave **3** (820 mg, 80%) as white prisms: mp 204−206 °C; ^{1}H NMR (acetone-d_6) δ 3.57 (m, 2H), 3.74 (m, 2H), 3.96 (s, 3H), 6.88 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 7.25 (m, 1H), 7.27 (dd, J = 7.7, 8.2 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 22.2, 29.1, 53.5, 106.2, 118.8, 120.8, 125.6, 126.8, 131.9, 134.7, 155.8, 165.8; MS (EI) m/z 204 (M^+, 63), 159 (100), 144 (56), 127 (38), 115 (52), 63 (20), 51 (19). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H 5.92. Found: C, 70.44; H 5.82. The same procedure without the addition of ethanol afforded an 80:20 mixture of the 1,2-dihydro acid **4** and 1,4-dihydro acid **3**. Recrystallization afforded **4** as a white solid (64%): ^{1}H NMR ($CDCl_3$) δ 2.90 (dd, J = 7.8, 17.6 Hz, 1H), 3.23 (dd, J = 7.8, 17.6 Hz, 1H), 3.45 (m, 1H), 3.80 (s, 3H), 6.07 (dd, J = 2.2, 8.4 Hz, 1H), 6.50 (dd, J = 1.2, 8.4 Hz, 1H), 6.68 (d, J= 7.9 Hz, 1H), 6.75 (d, J= 7.9 Hz, 1H), 7.13 (t, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.2, 39.7, 55.4, 110.2, 119.2, 121.0, 124.7, 127.1, 129.0, 133.7, 156.2, 180.5.

Methyl 1,4-Dihydro-8-methoxy-2-naphthoate (5). The acid **3** (191 mg, 0.94 mmol) in MeOH (35 mL) was treated with ethereal diazomethane (**CAUTION**) until the solution remained yellow and TLC analysis revealed that no starting material remained. After addition of one drop of glacial AcOH to destroy the residual diazomethane, the solvent was removed in vacuo to afford an oily residue. Chromatography on silica gel (10% EtOAc/hexane) gave **5** as an oil in 95% purity (194 mg, 90%): ^{1}H NMR ($CDCl_3$) δ 3.53 (m, 2H, H1), 3.62 (m, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 6.73 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 7.5 Hz, 1H), 7.15 (m, 1H), 7.17 (dd, J = 7.5, 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 30.8, 51.7, 55.2, 107.4, 120.0, 122.4, 126.8, 128.0, 133.0, 136.1, 157.1, 167.4; MS (EI) m/z 218 (M^+, 51), 159 (100), 144 (61), 127 (31), 115 (56); HRMS (EI) m/z calcd for M^+, $C_{13}H_{14}O_3$ 218.0943, found 218.0942. The contaminant was methyl 8-methoxy-2-naphthoate (5%).

Methyl (2*R*,3*S*)-2,3-Dihydroxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoate (8). $K_3Fe(CN)_6$ (1.667 g), anhydrous K_2CO_3 (697 mg), $(DHQ)_2$−PHAL (26.5 mg, 0.2 equiv), and potassium osmate dihydrate (6.3 mg, 0.1 equiv) were vigorously mixed in a round-bottom flask, using two magnetic stirrer bars to grind the mixture. After 1 h a fine orange powder was formed. A portion of this mixture (162.5 mg) was added to a rapidly stirred solution of *tert*-butyl alcohol (1.15 mL), water (1.15 mL), and methanesulfonamide (11 mg) at room temperature. After stirring for 5 min, the solution was cooled to 0 °C and stirred until a thick orange-yellow slurry resulted (ca. 10 min). The ester **5** (25 mg, 0.115 mmol) was added in one portion and the heterogeneous slurry was stirred vigorously for 5 h at 4 °C. Solid Na_2SO_3 (ca. 150 mg) was added at room temperature and the mixture stirred for 1 h. After dilution with water, EtOAc was added. Upon separation of the layers, the aqueous layer was further extracted with EtOAc (×2). The combined organic layers were washed with 2 N KOH and brine, to remove the methanesulfonamide, and the solvent was removed in vacuo. Chromatography was carried out on silica (EtOAc/hexane) to remove the naphthoate contaminant and then 50% EtOAc/hexane was used to elute **8** as a white solid (24 mg, 85%); $[\alpha]^{20}_D$ +18.0° (c = 1.50, $CHCl_3$). The ee was determined to be 83%, using ^{19}F NMR analysis of the 3-Mosher ester. A sample of **8** was recrystallized from EtOAc/hexane to afford white prismatic needles, $[\alpha]^{20}_D$ +22.2° (c = 0.85, $CHCl_3$) [further recrystallizations did not change the optical rotation]: mp 149−151 °C; ^{1}H NMR ($CDCl_3$) δ 2.94−3.16 (m, 4H), 3.38 (br s, 1H), 3.79 (s, 3H), 3.88 (s, 3H), 4.26 (dd, J = 6.4, 10.6 Hz, 1H), 6.68 (d, J = 7.9 Hz, 1H), 6.73 (d, J = 7.9 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 33.9, 34.1, 53.3, 55.2, 69.9, 76.1, 107.4, 120.5, 120.9, 127.0, 134.9, 157.2, 176.1; MS (EI) m/z 252 (M^+, 6), 234 (16), 175 (100), 147 (41), 91 (37), 77 (26); HRMS (EI) m/z calcd for M^+, $C_{13}H_{16}O_5$: 252.0998, found 252.0998. Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H 6.39. Found: C, 61.73; H 6.72.

Benzyl 1,4-Dihydro-8-methoxy-2-naphthoate (6). Acid **3** (110 mg, 0.54 mmol) was added in one portion to a solution of *N*,*N*-carbonyldiimidazole (150 mg, 2 equiv) in CH_2Cl_2 (10 mL) at room temperature. Gas was evolved and the resultant solution was stirred for 30 min. Freshly distilled benzyl alcohol (59 μL) and DBU (84 μL) were added successively and the

(17) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (c) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165. (d) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(18) Walsh, P. J.; Sharpless, K. B. *Synlett.* **1993**, 605.

(19) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278.

(20) Ohta, S.; Shimabayashi, A.; Aono, M.; Okamoto, M. *Synthesis*, **1982**, 837.

(21) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(22) (a) Buisson, D.; Cecchi, R.; Laffitte, J.-A.; Guzzi, U.; Azerad, R. *Tetrahedron Lett.* **1994**, *35*, 3091. (b) Genêt, J. P.; Pfister, X.; Ratovelomanana-Vidal, V.; Pinel, C.; Laffitte, J. A. *Tetrahedron Lett.* **1994**, *35*, 4559.

(23) For general directions see Furber, M.; Mander, L. N.; Patrick, G. L. *J. Org. Chem.* **1990**, *55*, 4860.

solution stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 M HCl solution, water, 10% Na_2CO_3 solution, and brine. Evaporation of the solvent gave a white solid, which was chromatographed on silica gel (10% EtOAc/hexane) to afford **6** as a white solid in 90% purity (146 mg, 83%): ^{1}H NMR ($CDCl_3$) δ 3.53−3.70 (m, 4H), 3.85 (s, 3H), 5.28 (s, 2H), 6.73 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 7.7 Hz, 1H), 7.17 (dd, J = 7.7, 8.2 Hz, 1H), 7.20 (m, 1H), 7.30−7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.6, 30.8, 55.2, 66.2, 107.4, 120.0, 122.4, 126.8, 128.1, 128.5, 133.0, 136.3, 136.4, 157.1, 166.7; MS (EI) m/z 294 (M^+, 2), 203 (10), 202 (12), 159 (18), 115 (10), 91 (100). The contaminant was benzyl 8-methoxy-2-naphthoate (10%).

Benzyl (2*R*,3*S*)-2,3-Dihydroxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoate (9). The benzyl ester **6** was dihydroxylated using the method detailed for **5** except that as a consequence of the insolubility of **6** in the solvent system, toluene was added to the reaction mixture (*tert*-butanol:water:toluene, 16.7:16.7:2). The reaction was complete after 20 h. Chromatography on silica, using the same solvent systems as for **5**, gave **9** as a white solid (74%): $[\alpha]^{20}_D$ +2.1° (c = 1.30, $CHCl_3$). The ee was determined to be 92%, using ^{19}F NMR analysis on the 3-Mosher ester. A sample was recrystallized from ether to afford fine white needles, $[\alpha]^{20}_D$ +2.4° (c = 1.60, $CHCl_3$) [further recrystallizations did not change the optical rotation]: mp 145−147 °C; ^{1}H NMR ($CDCl_3$) δ 3.14−3.20 (m, 4H), 3.52 (br s, 1H), 3.79 (s, 3H), 4.31 (dd, J = 6.5, 10.2 Hz, 1H), 5.31 (AB system, δ_A = 5.28, δ_B = 5.34, J_{AB} = 12.3 Hz, 2H), 6.68 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 7.7 Hz, 1H), 7.14 (dd, J = 7.7, 8.1 Hz, 1H), 7.20−7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 34.0, 34.1, 55.2, 68.0, 69.9, 76.1, 107.5, 120.5, 120.9 , 127.0, 128.0, 128.5, 128.6, 134.8, 135.0, 157.2, 175.6; MS (EI) m/z 328 (M^+, 5), 310 (7), 220 (120), 176 (80), 148 (40), 91 (100). Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H 6.14. Found: C, 69.24; H 6.06.

(2*R*,3*S*)-2,3-Dihydroxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (10). A solution of benzyl ester **9** (300 mg) in EtOAc (15 mL) containing 5% Pd−C (15 mg) was stirred at room temperature under an atmosphere of hydrogen (balloon) for 23 h. The solution was filtered and evaporated to dryness, and the residue crystallized from acetone to give colorless prisms: mp 170−172 °C; ^{1}H NMR (acetone-d_6) δ 3.00−3.23 (m, 4H), 3.91 (s, 3H), 4.35 (dd, J = 6.3, 10.9 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 32.6, 32.7, 53.4, 68.4, 74.5, 106.0, 119.4, 120.0, 125.3, 134.5, 156.1, 174.9. Anal. Calcd for $C_{12}H_{14}O_5 \cdot H_2O$: C, 56.24; H 6.29. Found: C, 56.56; H 6.42.

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Supporting Information Available: Experimental procedures for the preparation of **1**, **7**, (±)-**8**, and 3-mono-Mosher esters of **8** and **9**, including NMR spectroscopic data (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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